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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,456	BALSCHMIDT ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) none is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-23 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/2/03 & 1/6/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-23 are pending.

The pending claims 1-23 are under examination in this Office action.

IDS

The references cited in the IDS filed 9/2/03 have been considered by Examiner.

The foreign patent references listed in IDS filed 2/27/04 have been considered by Examiner. However, Applicants' submission of the said IDS is incomplete since the non-patent reference "International search report" filed 10/22/03 is not submitted with the PTO-1449 form. Thus, the instant application fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. The information referred to therein has not been considered as to the merits. Examiner cannot find this non-patent reference in the file; and thus, it has been lined-through and is not considered by Examiner.

Specification/Claims Objection

The disclosure is objected to because of the following informalities:

(1) The specification is objected to because the last page of the specification filed 6/23/03 contains the claims 1-11. The specification and the claims should be set forth in separate sheets.

(2) On page 2, line 28, "methylsulfonylmethane **or** MSM" should be changed to "methylsulfonylmethane (MSM)".

(3) On page 3, lines 20-21, the peptide names, e.g., "GLP-1", "GLP-2", "Factor VII" and "Factor VIII" should be spelled out for the first instance of use; see also page 5, line 31, "HPLC".

(4) On page 6, lines 8-9, "Δ% Purity" should be clarified; does it refer to change in purity?

(5) Also, the specification is objected to because the specification sets forth the peptide analogs, e.g., *Lys(B28) Pro(B29)-human insulin*, without reciting the corresponding sequence identifier; the terms "B28" and "B29" need to be clarified to indicate whether they refer to insulin B-chain residues 28 and 29. Clarification in this regard throughout the specification is required.

(6) In claim 2, "the **amount** of dimethyl sulfone" should be changed to "the **concentration** of dimethyl sulfone" because "mM" is a unit of concentration but not unit of "amount" precisely; see also claim 3.

(6) In claims 12 and 15-23, the peptide analogues/derivatives, e.g., Asp(B28)-human insulin", "Lys(B28) Pro(B29)-human insulin", "$N^{\varepsilon B29}$-tetradecanoyl des (B30)-human insulin", "Gly(A21) Arg(B31)-human insulin", "$N^{\varepsilon B29}$-litocholoy-γ-glutamyl des (B30)-human insulin" "Gly(8)-human GLP-1" , "Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26) human GLP-1(7-37)OH", and "Gly(8)-human GLP-2" lack the corresponding peptide primary structure or/and amino acid sequence identifiers.

In claim 20, "$N^{\varepsilon B29}$-lito-choloyl-" should be changed to "$N^{\varepsilon B29}$-litho-choloyl-"".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 12-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 12, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 12 recites "a derivative of any such peptide or analogue". The specification does not define the **derivative of** the peptide **analogue**". Note that on page 2, lines 22-24, the specification has defined the derivative as an analogue of the parent peptide; and thus, said recitation "**derivative** (*analogue*) of ... **analogue**" is awkward and indefinite.

The dependent claims 13-23 are also rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1 and 4-11 are rejected under 35 U.S.C. 102 (b) as being anticipated by Jacob, E. (EP 1052288 A1, from the IDS).

In the patent claims 1 and 15-17, Jacob discloses a pharmaceutical composition comprising dimethylsulfone (claim 17) and a polypeptide (claim 1), which anticipate instant claim 1.

In the patent claims 18-19, Jacob teaches that the above-mentioned composition is suitable for intramuscular, inhalation, intratracheal instillation, aerosolization and/or topical administration routes, which anticipate instant claims 6-11.

On paragraph [0037], Jacob teaches that the composition is prepared as a solution or suspension (in dispersion media), which anticipates instant claims 4-5.

Claims 1, 4 and 6-12 are rejected under 35 U.S.C. 102 (b) as being anticipated by Braun, S. (EP 1254961 A1, from the IDS).

In the patent claims 11 and 21, Braun teaches a pharmaceutical composition comprising interleukin-10 polypeptide (claim 11) and dimethylsulfone (claim 21), which anticipate instant claims 1 and 12.

In Example 3, Braun teaches that the composition is in a solution, which anticipates claim 4.

In the patent claims 4-5, Jacob teaches that said composition is suitable for intramuscular, inhalation, intratracheal instillation, aerosolization and/or topical administration routes, which anticipate instant claims 6-11.

Claims 1, 4-6 and 11-12 are rejected under 35 U.S.C. 102 (a) as being anticipated by Marini J. L. (US Pat. No. 6328987 B1).

In the patent claim 1-3, Marini teaches a composition comprising a peptide and methylsulfonylmethane (MSM, i.e., dimethyl sulfone), which anticipate instant claim 1.

On column 3, lines 17-24 and columns 4-5, Marini teaches that the composition is aqueous solution or suspension, which anticipates instant claims 4-5.

In the patent claims 7-8, Marini teaches that topically administering the composition comprising MSM and human alpha interferon 2 peptide to a subject skin, which anticipates instant claims 6 and 11-12.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4-11 are rejected under 35 U.S.C. 102 (b) as anticipated by or, in the alternative as obvious under 35 U.S.C. 103(a) over Herschler, R. J. (US Pat. No. 4559329, from the IDS). Although the invention is not identically disclosed or described as set forth in 35 U.S.C. 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a designer having ordinary skill in the art to which said subject matter pertains, the invention is not patentable.

In Example IX, Herschler teaches a pharmaceutical composition comprising MSM (see the above) mixed with food containing peptides/polypeptides, which is applied to instant claim 1.

In the patent claim 6, Herschler teaches that the composition is suspended or dissolved in MSM, as applied to instant claims 4-5.

On columns 4 (line 33) to column 5 (line 46), Herschler teaches that the composition is administered intraperitoneally, intravenously or parenterally, orally, and/or by inhalation, which is applied to instant claims 6-11.

Claims 1-11 are rejected under 35 U.S.C. 102 (b) as anticipated by or, in the alternative as obvious under 35 U.S.C. 103(a) over Herschler, R. J. (US Pat. No. 4973605, from the IDS). Although the invention is not identically disclosed or described as set forth in 35 U.S.C. 102, if the differences between the subject matter sought to be patented and the prior art are such that

the subject matter as a whole would have been obvious at the time the invention was made to a designer having ordinary skill in the art to which said subject matter pertains, the invention is not patentable.

In Examples 16 and 18, Herschler teaches a pharmaceutical composition comprising MSM (see the above) mixed with food containing peptides/polypeptides, which is applied to instant claim 1.

In Example 28, Herschler teaches suitable MSM concentration is about 10.9 mg/ml; considering MSM molecular weight is 90.08, 10.9 mg/ml $\approx$ 0.121 M, i.e., 121 mM, which meets the limitations of instant claims 2-3.

In Example 16, Herschler teaches that the composition is dissolved in aqueous solution, as applied to instant claim 4.

On column 9, lines 35-39, Herschler teaches the composition comprising MSM admixed in crystalline (particle) form with foodstuff an aqueous, i.e., in suspension, which is applied to instant claim 5.

Herschler teaches intravenous (columns 14-15), oral (Example 21), and parental injection (column 10, line 34) administration of the composition, which anticipates instant claims 6-9 and 11.

Also, Herschler teaches inhalation route for administering the composition (column 10, lines 22-26), which anticipate instant claim 10.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action has been set froth above.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herschler, R. J. (US Pat. NO. 4973605, from the IDS) taken with Herschler et al. (US Pat. No.3551554), Ertl et al. (US Pat. No. 6686177 B1), Brader M. L. et al. (US Pat. No. 6465426 B2), Habermann et al. (US Pat. No. 6534288 B1), Havelund et al. (US Pat. No. 5750497), Knudsen et al. (US 201/0011071 A1), Knudsen et al. (US Pat. No. 6939853 B2), and Drucker D. J. (US Pat. No.5952301).

The teachings of Herschler applied to instant claims 1-11 have been discussed above.

Yet, Herschler does not expressly teach the pharmaceutical composition comprising MSM (see above) and insulin and GLP-1 peptides.

In Example 76, Herschler et al. (3551554) teach a pharmaceutical composition comprising insulin and dimethyl sulfide (DMSO) wherein DMSO has ability of enhancing penetration of the insulin through the subject cells, as applied to instant claim 12.

Ertl et al. et al. teach a pharmaceutical composition comprising the human insulin analog useful for treating diabetes, wherein the said analog is Gly(A21)-Arg(B31)-Arg(B32) human insulin (see the patent claims 28 and 29), which is applied to instant claims 13-14 and 19.

In the patent claim 32 and column 13, lines 43-45, Brader et al. teach a composition comprising human insulin analog, i.e., Asp(B28) human insulin, as applied to instant claim 15.

In the patent claims 7 and 49, Brader et al. teach a composition comprising human insulin analog, Lys(B28)Pro(B29), as applied to instant claim 16.

In the patent claims 1 and 4, Habermann et al. teach human insulin analog, Lys(B3)Glu(B29) which has improved folding property thus control for the enzymatic processing is simplified (see column 3, lines 6-13). The Habermann et al. teachings are applied to instant claim 17.

In the patent claims 79 and 88, Havelund et al. teach a pharmaceutical composition comprising B29-Nε-teradecanoyl des(B30) human insulin, as applied to instant claim 18.

In Example 25, Havelund et al. teach B29-Nε-lithocholoyl-L-glutamyl des(B30) human insulin, as applied to instant claim 20.

In the patent claim 74, Knudsen et al. (2001/0011071) teach a pharmaceutical composition (see column 7) comprising an glucagon like peptide-1 (GLP-1) analog wherein amino acid residue of GLP-1 is glycine, i.e., Gly (8)GLP-1, said analog is human GLP-1 peptide (see [0002]), which is applied to instant claim 21.

In Example section (columns 11-12), Knudsen et al. (6939853) teach a pharmaceutical composition (see column 7) comprising Arg(34), Nε-(γ-Glu(N^{α}-hexadecanoyl))-GLP-1(7-37) for treating Dyslipidemia, as applied to instant claim 22.

Drucker teaches a pharmaceutical composition comprising human GLP-2 analog, i.e., Gly(2)-**h**GLP-2 peptide (see Example 3) which stimulates tissue/cell growth (see abstract), as applied to instant claim 23.

One of ordinary skill in the art at the time the invention was made would have substituted DMSO with MSM, and would have chosen the above-mentioned insulin analogs, GLP-1 or/and GLP-2 analogs and formulated them with MSM in said pharmaceutical composition. The skilled artisan would have been motivated to do this because the insulin

analogs, and GLP-1 and GLP-2 analog have useful properties or/and attractive advantages, e.g., the Ertl's insulin analogs are directed to the enhanced zinc binding (which enhances insulin receptor activity and augments physiological potency of insulin); and, the Havelund's insulin analogs are directed to enhance biological half-life of insulin; and also because of the following reasons.

(1) MSM has potential of improving or/and reducing degree of condition associated with diabetic state as taught by Herschler (see Example 20).

(2) MSM is structurally and chemically analogue to DMSO; and thus it is best candidate for substitution for DMSO in the above-mentioned Herschler et al. (3551554) pharmaceutical composition. This is because MSM is a metabolite of dimethyl sulfoxide (DMSO); unlike many other sulfur-containing chemical compounds, MSM is inert and **non-toxic**, and its aqueous solutions can be used as a blood diluent (see column 14, lines 48-51, Herschler (4973605)), especially useful for storage for unstable pharmaceutically active agents (see column 1, lines 46-48, Herschler's patent). In addition to the above-stated pharmacologically beneficial effects of MSM, it is useful in treating a surprising variety of other diseases and adverse physiological conditions (see column 2, lines 46-52, Herschler's patent); e.g., MSM is effective to relieve pain and reduce stress-induced death in animal (see abstract of the Herschler's patent).

(3) Also, MSM per se is a key nutritional ingredient to mammals including human (see column 4, Herschler's patent).

(4) MSM has been demonstrated to be safely administered by a variety of administration routes as taught by Herschler (column 10).

Thus, the skilled artisan would have formulated the therapeutically active peptide, insulin or GLP-1 (see the above statement) with MSM which is clinically safe, stable, non-toxic to animal, suitable for formulation of relatively unstable bioactive molecules in addition to that MSM per se can help in treatment of the disorder states (see the above), and had the claimed pharmaceutical composition in hand when the invention is made with successful expectation.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel W. Liu, Ph.D.
January 10, 2006

Jon P. Weber, Ph.D.
Primary Examiner